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COMMUNICATION

Bimetallic Cu-Mn B spinel oxide catalyzed oxidative synthesis of 1,2-disubstituted benzimidazoles from benzyl bromides

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Rohit Sharma,[a#] Firdoos Ahmad Sofi,[a#] Preeti Rana,[a] Prasad V. Bharatam[a]*

Cu-Mn B, (a heterogeneous catalyst) catalyzed synthesis of 1-benzyl-2-phenyl-1H-benzo[d]imidazolesis reported. In this reaction, 2-phenyl-1H-benzo[d]imidazoles are found to be the side products. Reported protocol is simple, highly efficient, tolerates wide variety of substrates and products were formed in good to excellent yield.

The 1,2-disubstituted benzimidazoles are privileged scaffold present in various natural and medicinally important compounds. This type of scaffold is also present in various types of marketed drugs as well.[1-4] These are one of the most important *N*-heterocycles in terms of drug discovery perspective.[5-7] The therapeutic application of these compounds are reported in hypertension,[8] obesity,[9] HIV,[7] HSV-1[10] and influenza.[11] Thus, the development of efficient methods for the synthesis of 1,2-disubstituted benzimidazole scaffold is of utmost importance in organic synthesis.

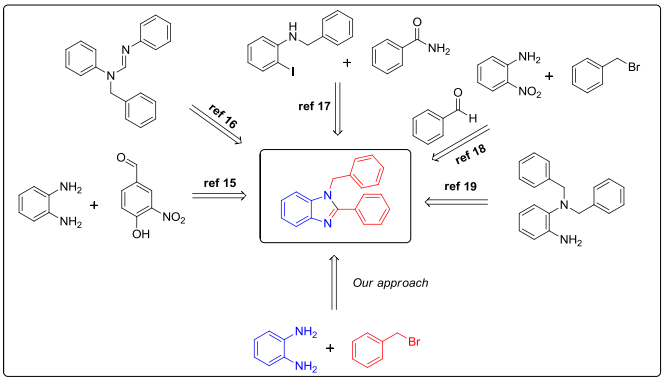

Figure 1. Previous methods and our approach.

Various methods were reported in literature for the synthesis of benzimidazole scaffold, [12-14] but only a few methods were reported for the synthesis of 1,2-disubstituted benzimidazoles, these include condensation of *o*-phenylenediamine with aldehyde,[15] C-H amination reaction of *N,N*´-diphenyl formamidine,[16] coupling reaction between *N*-benzyl-2-iodoaniline and benzamide,[17] reaction of 2-nitroaniline with benzyl bromide and aldehyde[18] and acceptorless dehydrogenative coupling of tertiary amines and arylamines.[19] But, all these reported methods suffer from various drawbacks, such as the use of harsh reaction conditions, low substrate scope, lower yields and longer reaction times. Based on these reports, we started working towards the synthesis of 1,2-disubsituted benzimidazoles by using bimetallic Cu-Mn catalyst available with us. Cu-Mn B catalyst is prepared by using literature reported method.[20] This catalyst has been used in various organic transformations which involves Chan-Lam type of coupling reaction for C-N bond formation,[21] Husigen cyclo addition reaction,[20] regioselective halogenations of phenols and *N*-heterocycles,[22] synthesis of imidazopyridine scaffold,[23] synthesis of amides[24] and in nitrogen insertion reaction for the synthesis of quinazolinones.[25] Inspired from previous literature reports and our ongoing interest for the synthesis of *N*-heterocycles,[24, 25] we started working towards exploring catalytic application of Cu-Mn spinel oxide for the synthesis of *N*-heterocycles.

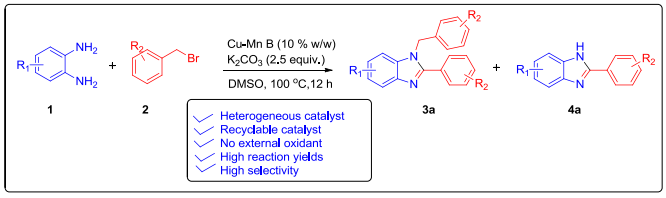

Figure 2. Cu-Mn B catalyzed synthesis of 1-benzyl-2-phenyl-1H-benzo[d]imidazole and 2-phenyl-1H-benzo[d]imidazole.

Initial attempt was to utilize Cu-Mn B catalyst for the synthesis of 1-benzyl-2-phenyl-1H-benzo[d]imidazole. After getting insight from literature for the synthesis of 1-benzyl-2-phenyl-1H-benzo[d]imidazole, it was found suitable to utilize *o*-Phenylenediamine and benzyl bromide as starting material. Firstly, model reaction was conducted using Cu-Mn B as catalyst, in the presence of ligand L-proline, DMSO and K_2CO_3 under reflux conditions for 12 h, but we were able to isolate desired product in 25 % yield with the formation of 2-phenyl-1H-benzo[d]imidazole **4a** as well in 40 % yield. Further reaction was conducted without using

[a] Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research. S.A.S Nagar-Mohali-160062
[#] These authors contributed equally
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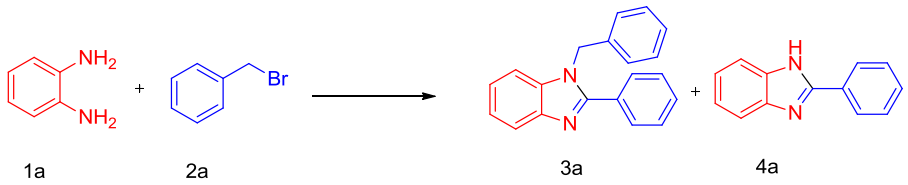
ligand. To our surprise, the desired product **3a** was formed in 68 % yield and 2-phenyl-1H-benzo[d]imidazole **4a** was formed in 20 %.

Table 1. Solvent and catalyst optimization studies[a]



1a 2a 3a 4a

Entry	Catalyst(% (w/w)	Temp. (ºC)	Base(equiv)	Time (h)	Solvent	Ligand(equiv)	%Yield[a](3a/4a)
1.	$CuCl_2$(10)	110	K_2CO_3 (3)	12	DMSO	None	0
2.	$CuCl_2$ (10)	110	K_2CO_3 (3)	12	DMSO	L-proline (20)	0
3.	CuO (10)	110	K_2CO_3 (3)	12	DMSO	None	Trace
4.	$Cu(OAc)_2$(10)	110	K_2CO_3 (3)	12	DMSO	None	(15:40)
5.[b]	**Cu-Mn B (10)**	110	K_2CO_3 (3)	12	DMSO	None	**(68:20)**
6	Cu-Mn B (20)	110	K_2CO_3 (3)	12	DMSO	None	66:18
7.	Cu-Mn B (10)	110	K_2CO_3 (3)	12	DMSO	L-proline (20)	(25:40)
8.	CuO (10)	110	K_3PO_4 (3)	12	DMSO	None	trace
9.	$Cu(OTf)_2$	110	K_2CO_3 (3)	12	DMSO	None	0
10.[c]	Cu-Mn B (10)	110	K_2CO_3 (3)	12	DMSO	None	50:10
11.[c]	Cu-Mn B (10)	110	K_2CO_3 (3)	12	Toluene	None	0:50
12.[d]	Cu-Mn B (10)	110	K_2CO_3 (3)	12	DMSO	None	50:50
13	Cu-Mn B (10)	90	K_2CO_3 (3)	12	Water	None	0:10
14.	Cu-Mn B (10)	110	K_2CO_3 (3)	12	DMF	None	10:40

Reagents and conditions: *o*-phenylenediamine **1a** (1 equiv.), benzyl bromide **2a** (2 equiv.), Cu-Mn B (10% w/w), K_2CO_3 (2.5 equiv.), DMSO (3mL); [a]isolated yield; [b]optimized reaction condition; [c] under N_2 atmosphere; [d] under O_2 atmosphere

The separation of the two products in column chromatography has been found to be easy because of their distinguishable R_f values. In this reaction selectivity for **3a** was achieved by 77 %. Further screening of the catalytic reaction was done by using various solvents such as toluene, DMF and water but none of them found to be efficient for this transformation. We also tried Cu (I) and Cu (II) catalyst for this transformation but none of them found suitable. Cu-Mn B was found to be suitable catalyst for this transformation. This might be due to distinct Cu-Mn B phase as shown in previous literature reports based on PXRD.[24] Also, in case of Cu-Mn B, as revealed in XPS analysis, these metals exit in multiple oxidation states (Cu^{+2}, Mn^{+2}, Mn^{+3} and Mn^{+4}) in bimetallic Cu-Mn catalyst. Having optimized reaction conditions in hand, next we tried to explore substrate scope of reaction for various substituted benzyl bromides, reaction works well with all substituted benzyl bromides bearing electron withdrawing (Figure 3 entry, **3d, 3e** and **3f**) as well as electron donating group (Figure 3 entry, **3b, 3c** and **3g)**

Yields in case of electron withdrawing groups (Figure 3 entry **3d, 3e** and **3f**) in benzyl bromides are slightly higher in comparison to electron donating groups (Figure 3 entry, **3b, 3c** and **3g**). Also, we tried various substituted OPDs (*o*-Phenylenediamine) bearing electron withdrawing (Figure 3 entry **3h, 3i, 3j, 3k** and **3p**) and electron donating groups (Figure 3 entry **3l, 3m** and **3n**) as well as di- substituted OPDs (Figure 3 entry **3o** and **3p**).

Apart from that, strong electron withdrawing group, such as 5-nitro OPD (Figure 3 entry, **3h** and **3i)** was also tried in this reaction. The reaction works well with all types of substituted OPDs giving corresponding product in good yields. In case of electron withdrawing groups in OPDs (Figure 3 entry **3h, 3i, 3j, 3k** and **3p**), yields are lesser in comparison in electron donating groups (Figure 4 entry **3l, 3m** and **3n**).

Benzyl bromide bearing substituents in *meta* position (Figure 3, entry **3c, 3f** and **3i**) gave slightly lower yield in comparison to *para* substituents (Figure 3, entry **3b, 3d, 3e, 3g, 3k, 3n** and **3o**). Also, in case of OPD bearing disubstituted 4,5-dichlorobenzene-1,2-diamine (Figure 3 entry **3p**) reaction works well giving corresponding product in good yield. No particular electronic effect was seen in the synthesis of 2-aryl benzimidazole.

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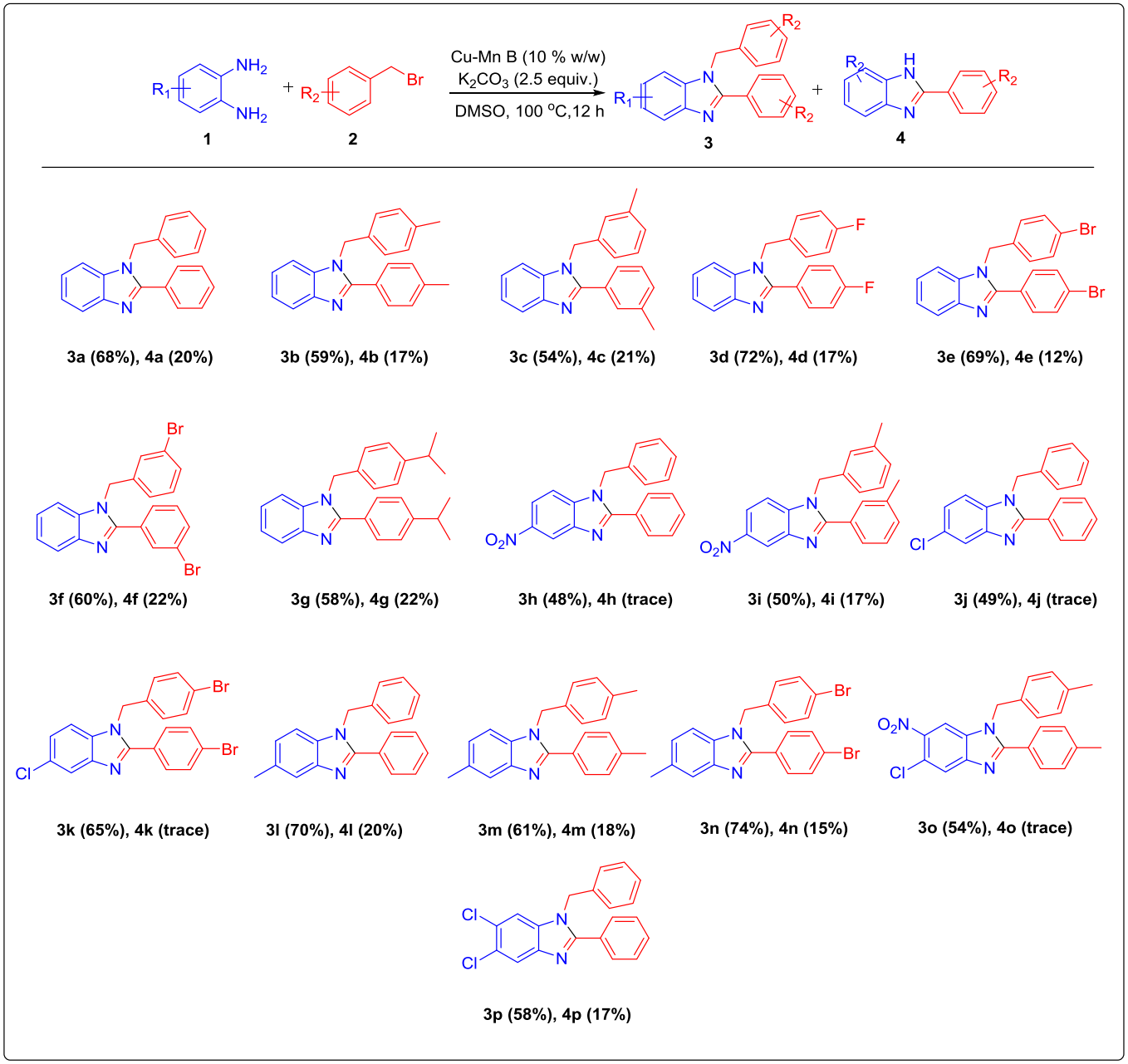

Reagents and conditions: OPD **1a** (1 equiv.), benzyl bromide **2a** (2 equiv.), Cu-Mn B (10 %w/w), K_2CO_3 (3 equiv.), DMSO (3 mL), 110 °C, 12 h

Figure 3. Substrate scope of reaction by using substituted OPD and benzyl bromides.

A plausible mechanism of reaction can be proposed (Figure 4), which involves initial Ullmann type of coupling between OPD and benzyl bromide leading to the formation of the doubly *N*-alkylated intermediate **I**. Oxidation of benzylic carbon in intermediate **I** leads to the generation of iminic intermediate **II**. Subsequently, cyclization happens due to the nucleophilic attack of benzylic nitrogen at the iminic carbon centre, leading to the formation of intermediate **III**. Additional oxidation step leads to the formation of final product **3a**. Mono substituted benzimidazole, intermediate **IV** also may be formed in the initial step, yielding 2-aryl benzimidazole **4a** along a similar pathway. Formation of compound **3a** from the preformed **4a** is also possible in the same catalytic condition as evidenced by the control experiment.

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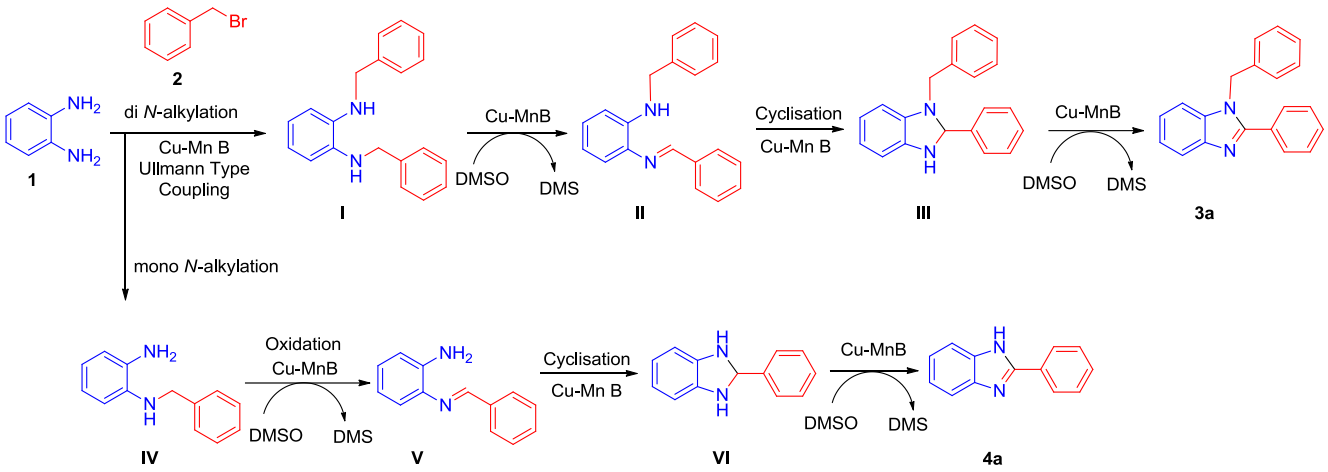
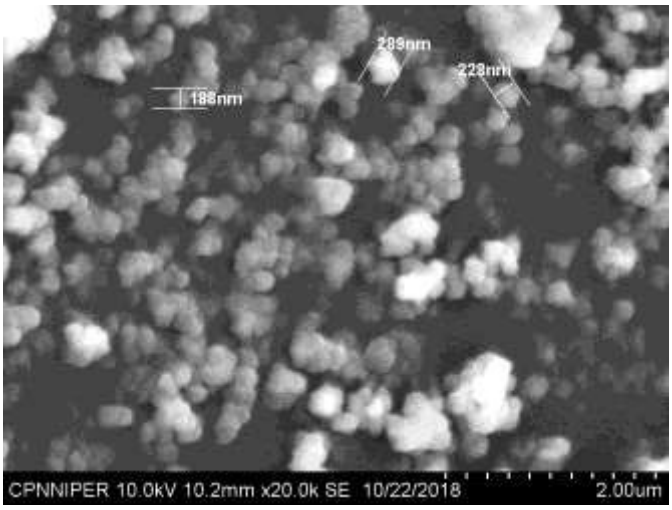
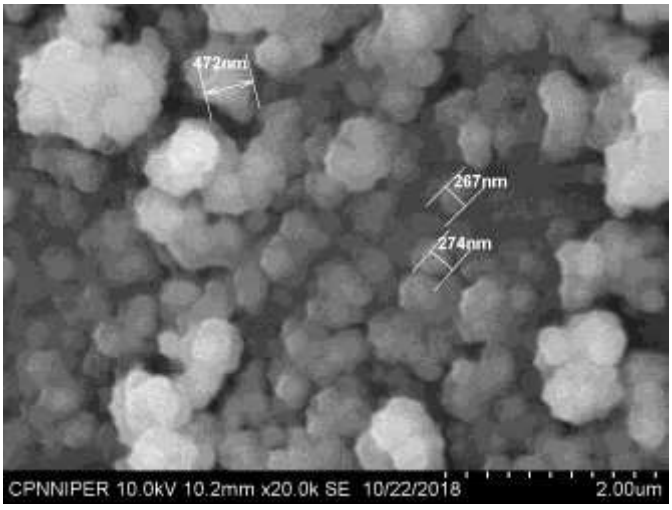


Figure 4: Plausible mechanism for the generation of title compounds



(a)



(b)

Figure 5: SEM analysis images before (a) and after use (b).

Next, we tried to check the recyclability of catalyst. The catalyst was recovered by filtration after every reaction and reused for four successive reactions for the synthesis of 2-Aryl-*N* benzyl benzimidazole **3a** without loss of significant activity. The % yields over 4 cycles were 68, 65, 60 and 55 %. The reduction in the yields during recycling process may be attributed to the limitations in the catalyst recovery. Further, in order to know the surface morphology of catalyst and size of Cu-Mn B nanoparticles, Scanning electron microscopy analysis shows that surface morphology of the catalyst remains same before and after four cycles of reaction also size of nanoparticles remains same.

In summary, we have developed an efficient method for the synthesis of 1,2-disubstituted benzimidazoles using bimetallic catalyst in one pot. Further, reaction has wide substrate scope, various functional groups are well tolerated and catalyst can be reused up to four cycles. The side product 2-aryl benzimidazole also can be isolated, though in small yields.

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